99-7; 31·$^3/_2$ oxalate, 123837-27-4; 32, 51627-76-0; 33, 114725-06-3; 33·2HCl, 123837-13-8; 34, 122829-77-0; 35a, 123837-00-3; 35b, 123837-10-5; 35c, 114724-65-1; 36a, 122829-26-9; 36b, 122829-29-2; 37a, 122829-60-1; 38, 114724-81-1; 38·HCl, 114724-80-0; 39, 123837-01-4; 40, 123837-02-5; 40·oxalate, 123837-24-1; 41, 123837-25-2; 41·oxalate, 123837-26-3; $H_3CC(=NOH)NH_2$, 22059-22-9; $EtC(=NOH)NH_2$, 29335-36-2; $PhCH_2C(=NOH)NH_2$, 19227-11-3; $H_3CC(=NOH)CH_3$, 127-06-0; $HC\equiv CCH_2NH_2$, 2450-71-7; $HONHC(NH_2)=NH$, 6345-29-5; $EtOCOC(=NOH)NH_2$, 10489-74-4; PhMgBr, 100-58-3; $MeNHC(=NH)NHOH$, 123837-29-6; $Me_2NC(=NH)NHOH$, 29044-27-7; 3-quinuclidinone, 3731-38-2; 2-bromo-5-methylfuran, 123837-09-2; 2-bromofuran, 584-12-3; 2-bromo-4-methylfuran, 78259-59-3; 3-(4-methylfuran-2-yl)-2,3-dehydroquinuclidine, 123837-11-6; N-[(1-methoxyethylidine)amino]-3-quinuclidinecarboxamide, 123837-14-9; 3-(N-hydroxyamidino)quinuclidine, 123837-16-1; quinuclidine-3-carboxylic acid hydrochloride, 6238-34-2; oxazole, 288-42-6; α-(tetrahydroxypyranyloxy)benzyl cyanide, 41865-47-8; 3-(methoxycarbonyl)-2,3-dehydroquinuclidine, 31539-88-5; 4-methyloxazole, 693-93-6.

Supplementary Material Available: Table of microanalytical data for novel compounds (2 pages). Ordering information is given on any current masthead page.

Synthesis and α_2-Adrenoceptor Effects of Substituted Catecholimidazoline and Catecholimidazole Analogues in Human Platelets

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It is known that the steric requirements for the interactions of catecholamines and catecholimidazolines with α_1- and α_2-adrenoceptors are different. New analogues of desoxycatecholimidazoline (1), desoxycatecholimidazole (3), benzylic hydroxyl substituted imidazole (4), and the aromatic fluorine substitution analogues of 1 at the 2 (5), 5 (6), and 6 (7) positions, and a set of asymmetric 4-substituted catecholimidazolines, S-8 and R-8, were prepared and tested for interaction with α_2-adrenoceptors in human platelets. With the exception of 3, all compounds were selective for α-adrenoceptor-mediated responses in human platelets. Introduction of a double bond in imidazoline 1 to give an imidazole 3 or the introduction of a benzylic hydroxyl group to 3, as in 4, reduced the inhibition of platelet aggregation with a rank order potency of 1 > 3 > 4. Fluorine atom substitution at the 2-, 5-, or 6-positions only slightly modified the inhibitory activity of 1. Each analogue (1, 3–7) produced α_2-mediated inhibition of platelet adenylate cyclase and can be classified as a partial agonist. The inhibition potency of S-8 and R-8 against epinephrine-induced aggregatory responses were greatly different, and only R-8 and 4 were α_2-agonists on human platelet function. Our studies provide further evidence for the differential interaction of catecholamines and catecholimidazolines in α_1- and α_2-adrenoceptor systems.

Phenethylamines and benzylimidazolines constitute the two major classes of drugs that are known to interact with α-adrenoceptors.[1] In our previous studies we have found 3,4-dihydroxytolazoline (1) to be a potent full agonist on α_1-adrenergic receptors while it has shown only partial agonist activity on α_2-adrenoceptors. We have found that the introduction of a hydroxyl group at the benzylic position of 1 to give 3,4,α-trihydroxytolazoline (2) leads to a compound with full agonist activity on the α_2-adrenergic receptor but brings about a reduction in affinity for α_1-adrenoceptor activity. Moreover, the phenylethylamines always follow the Easson–Stedman theory, while imidazolines do not.[2,3] Thus, the structure–activity relationships for activation of α-adrenergic receptors within the imidazoline class are considerably different from that of phenylethylamines.

The present study was directed at investigating the effects of structural modification of 3,4-dihydroxytolazoline on α_2-adrenergic activity in human platelets. It has been shown previously that certain imidazole derivatives do possess potent and selective antagonist activity on α_2-adrenergic receptors.[4] We have also prepared and investigated the replacement of the imidazoline ring of 1 with an imidazole group to give 3 and we also added a hydroxyl group to give 4 so we could compare its activity to that in the imidazoline series. Fluorine substitution on norepinephrine,[5] a classical phenylethylamine compound, resulted in a 2-fluoro analogue that was a selective agonist for β-adrenergic receptors, while the 6-fluoro analogue was a selective agonist on α-adrenergic receptors. Our objective was to prepare 2-, 5-, and 6-fluoro analogues of 1 to give 5, 6, and 7, respectively, and to investigate the effect of fluorine substitutions on α_2-adrenoceptor activity. Due to the paucity of information available on 4-substituted imidazolines in which the 4-substituent possessed a catechol functional group, we prepared the R and S isomers of 4-(3,4-dihydroxybenzyl)imidazoline (8). These three sets of analogues were studied in human platelets for α_2-adrenergic activity as agonists or as antagonists of epinephrine-mediated responses.

Chemistry

Synthesis of imidazoles 3 and 4 is outlined in Scheme I. N-(Diethoxymethyl)imidazole[6] (9) was treated with

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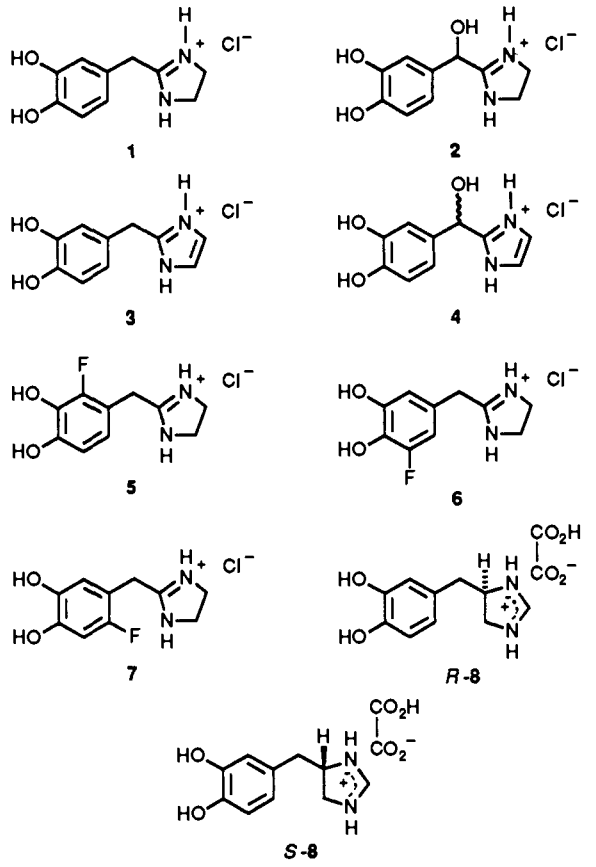
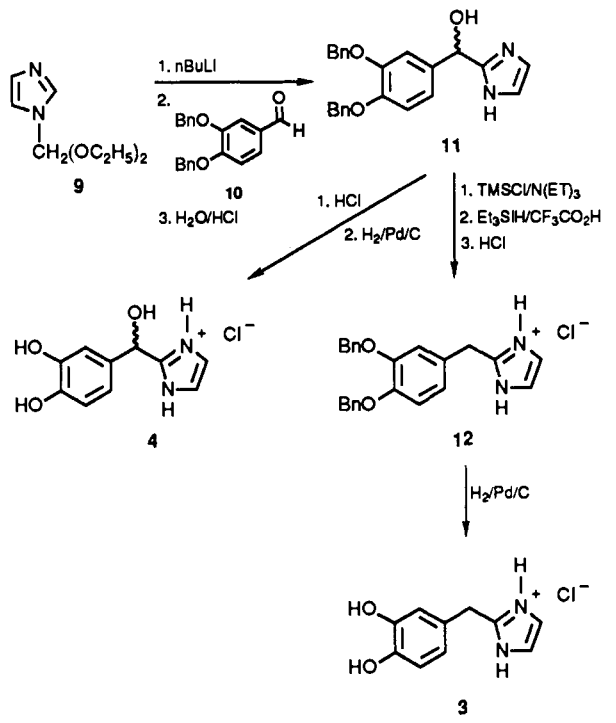


n-butyllithium followed by 3,4-bis(benzyloxy)benzaldehyde (**10**) to give the hydroxy imidazole **11** in 74% yield. Catalytic reduction of **11** provided the catechol analogue **4**. Treatment of **11** with trimethylsilyl chloride followed by triethylsilane in trifluoroacetic acid for 3 days gave the desired benzylic reduction to **12** in an overall yield of 47%. Reduction of the unprotected alcohol **11** directly with triethylsilane in trifluoroacetic acid gave a low yield (12%) of the desired **12**. Catalytic reduction of **12** gave the desired catechol **3**.

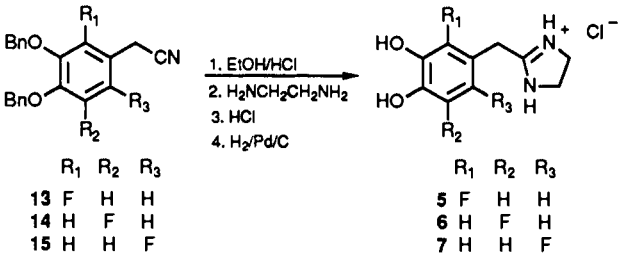
In Scheme II we illustrate the conversion of the nitriles **13**,[7] **14**,[8] and **15** to the desired catechols **5**, **6**, and **7**. Although we had previously reported the synthesis of nitriles **13** and **14**, we would now like to outline the synthesis of **15** in Scheme III. Treatment of **16** with formaldehyde and HCl followed by sodium cyanide gave the nitrile **17**. Boron tribromide was allowed to react with **17** to give the catechol, which was then benzylated to give **15**.

The synthesis of (*S*)-4-(3,4-dihydroxybenzyl)imidazoline from (*S*)-3,4-dihydroxyphenylalanine (L-DOPA) is illustrated in Scheme IV. L-DOPA was converted to the BOC-L-DOPA methyl ester according to the procedure of Banerjee and Kessler[9] (**19**). The ester **19** was benzylated,[8] hydrolyzed, and converted to the amide **20**.[10] The BOC protecting group was removed from **20** with trifluoroacetic acid[11] and the amide portion reduced with diborane[12] to give the diamine dihydrochloride **21**. The conversion of

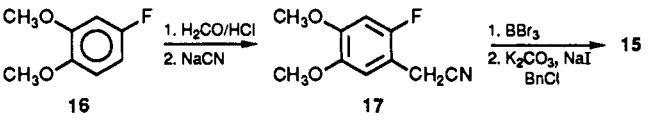
Scheme I



Scheme II



Scheme III



the diamine **21** to the imidazoline **22** was carried out with ethylformamidinium chloride[13] and the product was isolated as an oxalate salt. Debenzylation via catalytic hydrogenation of **22** gave the desired catechol **9**. We carried out a similar set of reactions starting with D-DOPA to obtain the *R* isomer of **8**.

Biological Results

Our preliminary studies compared the antagonist properties of the catecholimidazoline (3,4-dihydroxytolazoline, **1**) and catecholimidazole analogues (**3**, **4**) against epinephrine-induced aggregation and/or secretion (Table I). Compound **1** was approximately 5- and 3-fold more potent than desoxycatecholimidazole (**3**) as an inhibitor of primary and secondary aggregation to epinephrine, respectively. In contrast to **3**, the α-hydroxy analogue **4** was found to be both an antagonist and agonist of platelet activation. Analogue **4** was at least 10-fold more potent as an agonist than as an antagonist of epinephrine-induced responses in human platelets. In addition, **4** exhibited a

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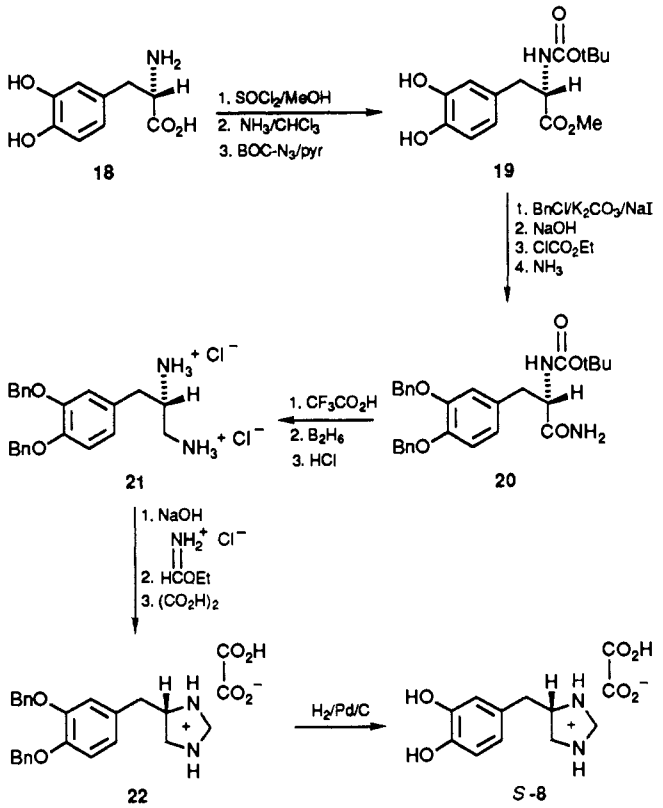
Table I. α-Adrenoceptor-Related Parameters for Analogues of Imidazole and Imidazoline in Human Platelets: Stimulatory or Inhibitory Activities against Epinephrine-Induced Platelet Aggregation (AGG) or Serotonin Secretion (SEC)

compd	pIC_{50} ± SEM[a] primary wave AGG	secondary wave AGG	serotonin SEC	pEC_{50} ± SEM:[b] primary wave AGG
1	4.58 ± 0.23 (4)[c]	4.77 ± 0.18 (4)	nd[d]	e
3	3.88 ± 0.12 (4)	4.28 ± 0.07 (4)	4.44 ± 0.08 (4)	e
4	3.20 ± 0.05 (4)	3.16 ± 0.02 (4)	3.36 ± 0.15 (4)	4.41 ± 0.08 (4)
5	4.40 ± 0.16 (6)	4.68 ± 0.25 (4)	4.81 ± 0.19 (3)	e
6	4.21 ± 0.16 (6)	4.18 ± 0.13 (3)	4.74 ± 0.13 (3)	e
7	4.51 ± 0.16 (6)	4.56 ± 0.34 (4)	4.56 ± 0.16 (4)	e
S-8	5.10 ± 0.18 (8)	nd	nd	e
R-8	3.28 ± 0.13 (7)	nd	nd	5.29 ± 0.28 (4)
(±)-8	4.56 ± 0.18 (4)	nd	nd	e

[a] $pIC_{50} = -\log IC_{50}$ where IC_{50} is equal to the molar concentration of compound which inhibits the response by 50%. Inhibitors were added 1 min prior to epinephrine (1 μM) in human platelet-rich plasma. Aspirin (1 mM) was included for determination of primary wave aggregation. [b] $pEC_{50} = -\log EC_{50}$ where EC_{50} is equal to the molar concentration of compound which produces 50% of maximum response. [c] Values in parentheses indicate the number of experiments (n). [d] nd = not determined. [e] No activity up to 300 μM.

Scheme IV



monophasic wave aggregation in aspirin-treated platelet preparations and biphasic aggregation at high concentrations (>100 μM) in three of six platelet preparations without aspirin. The secondary and primary waves of aggregation induced by **4** were blocked by the presence of 1 mM aspirin and 10 μM yohimbine, respectively (data not presented).

Aromatic fluorine substitution of phenethylamines and benzylimidazolines has been shown to cause a selective reduction or no significant change in the potency of agonists in α- and β-adrenoceptor systems.[14,15] Similar to **1**, the 2-, 5-, and 6-aromatic fluorine-substituted derivatives (**5–7**) blocked both phases of aggregation and serotonin release induced by epinephrine with similar inhibitory potencies. These compounds blocked aggregation responses with IC_{50}s ranging from 17 to 66 μM. Comparing the parent **1** and fluoro catecholimidazolines used in this study, the rank order of inhibitor potency against primary wave aggregation induced by epinephrine was **1 = 7 = 5 > 6** (Table I).

Table II. Inhibition of ADP, Arachidonic Acid (AA), and U46619 Induced Platelet Aggregation (AGG) and Serotonin Secretion (SEC) by Analogue **3**

inducer	response	pIC_{50} ± SEM[a]
ADP[b]		
	AGG	3.58 ± 0.18
	SEC	3.46 ± 0.16
AA		
	AGG	3.18 ± 0.07
	SEC	3.18 ± 0.04
AA + phentolamine[c]		
	AGG	3.84 ± 0.08
	SEC	3.79 ± 0.09
U46619[d]		
	AGG	2.79 ± 0.03
	SEC	2.81 ± 0.09
U46619 + phentolamine[c,d]		
	AGG	3.13 ± 0.03
	SEC	3.09 ± 0.06

[a] Values represent data from three to five preparations. [b] Compound blocked only the secondary wave of aggregation to ADP. [c] Phentolamine (1 μM) was added 1 min prior to drug and 2 min prior to inducer additions to platelet-rich plasma preparations. [d] Platelet preparations were incubated with 1 mM aspirin.

To further evaluate the specificity of the inhibitory action of these compounds, we examined their effects on the prostaglandin-dependent pathway of platelet activation using ADP, arachidonic acid, and U46619 (a thromboxane A_2 mimetic) as inducers. With the exception of desoxycatecholimidazole (**3**) (Table II), none of these compounds (**1**, **5–7**) at concentrations up to 1500 μM, blocked the aggregation responses to ADP, arachidonic acid (AA), or U46619 (data not presented). With **3**, the aggregatory and secretory responses to AA, ADP (secondary wave), and U46619 were blocked in a concentration-dependent manner, and incubation with phentolamine produced a relatively small increase in the inhibitory potency of **3** against the aggregatory and secretory responses to U46619 and AA (Table II). In these same experiments, analogue **4** produced a stimulation of the aggregatory response to AA which was blocked in the presence of phentolamine, and had no effect on the aggregatory or secretory responses to ADP or U46619 (data not presented).

In platelets with elevated cAMP levels, the α_2-adrenoceptor properties of epinephrine are correlated, in part, to the inhibition of adenylate cyclase with a concomitant

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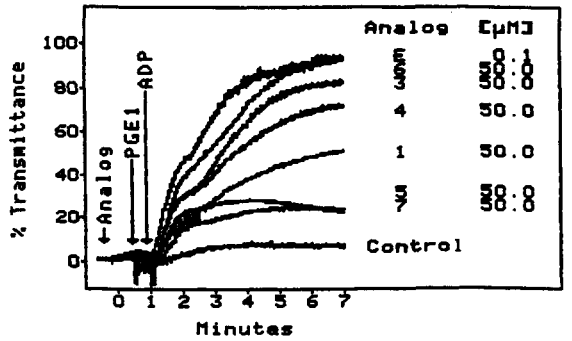

Figure 1. Blockade of prostaglandin E_1 (PGE_1, 1 μM) mediated inhibition of ADP-induced aggregation by epinephrine (E) and analogues of imidazole and imidazoline in human platelets. Control aggregation response was obtained in the presence of PGE_1 (1 μM) and ADP (3 μM) only.

reduction of platelet cAMP and potentiation of responses to inducers.[16,17] Using prostaglandin E_1 (PGE_1) as a stimulant of platelet adenylate cyclase activity, we found that epinephrine and each of the compounds reversed the PGE_1-mediated inhibition of ADP-induced platelet aggregation (Figure 1). The rank order of potency and percentage reversal by 50 μM of each analogue (n = 3–4) was **6** (70.6%) > **3** (53.7%) > **1** (32.4%) > **4** (28.9%) > **5** (17.7%) > **7** (7.5%). Epinephrine, at 0.1 μM, reversed PGE_1-mediated inhibition of ADP by 91.7% (Figure 1). Preincubation with phentolamine (1 or 10 μM) abolished the reversal of PGE_1-mediated effects by each analogue (**1**, **3**–**7**) on ADP-stimulated platelets (data not presented).

The *R* and *S* isomers and the racemate of **8** were found to exhibit inhibitory activity against primary wave epinephrine aggregation with a rank order of inhibitory potency of *S*-**8** > racemate ≫ *R*-**8**. *S*-**8** was 126-fold more potent than *R*-**8** as an antagonist of epinephrine-induced primary wave aggregation. In contrast, *R*-**8** was found to exhibit stimulatory activity at a concentration 100-fold less than that required for its blockade of epinephrine-induced aggregation. In this regard, the biphasic aggregation response of **8** was blocked by the presence of 1 mM aspirin (secondary wave only) and 10 μM yohimbine (data not presented). In these experiments, the EC_{50} (μM ± SEM) values of *R*-**8** for primary and secondary wave aggregation were 5.03 ± 0.20 (n = 5) and 4.89 ± 0.16 (n = 4). The amplitude of primary wave aggregation induced by *R*-**8** was 24.5 ± 0.9% transmittance, which corresponds well with that of epinephrine-induced aggregation. Primary aggregation induced by *R*-**8** was blocked by yohimbine with an IC_{50} of 1.1 μM (n = 3). In another study (n = 3), *S*-**8** was a competitive inhibitor of primary wave responses to epinephrine as assessed by Schild plot analysis giving pA_2, slope, and correlation coefficient values (mean ± SEM) of 5.49 ± 0.13, −0.96 ± 0.09, and 0.99 ± 0.01, respectively.

Discussion

Catecholamines activate human platelets through an initial interaction with α_2-adrenoceptors, leading to aggregatory and secretory responses.[18,19] By contrast, only a few reports have shown that synthetic benzylimidazoline analogues, including clonidine, are partial agonists in this experimental system,[19–21] and others have reported benzylimidazolines exhibit differing structure–activity relationships in α_1- and α_2-adrenoceptor systems.[2,3,15,22] In a previous report,[21] we found that the rank orders of stimulatory activity of catecholamines and catecholimidazolines in platelets were similar (*R* isomer > *S* isomer ≥ desoxy analogue), and that these observations differed from other reports of the interaction of benzylimidazolines in α_1- and α_2-adrenoceptor systems. In the present study, we observed that the majority of catecholimidazoline and catecholimidazole analogues were antagonists of epinephrine-mediated responses in human platelets. These results are qualitatively different from other reports with these compounds in the pithed rat and isolated rat vascular tissues.[14,15,23] Thus these findings suggest that the interaction of benzylimidazolines and catecholamines with α_2-adrenoceptors in platelets are different, and that further studies are required to evaluate the steric requirements for the activation of these receptors by benzylimidazolines.

The present study was done to expand on our understanding of the chemical specificity for interaction of selected catecholimidazoline and catecholimidazole analogues in human platelets. The analogues **1**, **3**, and **4** blocked epinephrine-induced aggregation with a rank order of antagonist potency (**1** > **3** > **4**). In addition, only **4** was found to be an agonist of platelet function. Both effects are presumably mediated by the activation of α-adrenoceptor sites since the biphasic aggregation response of **4** was blocked by the α_2-antagonist, yohimbine, and secondary wave aggregation was blocked by aspirin, an inhibitor of the metabolism of AA. In α_1-adrenoceptor tissues, analogues **1**, **3**, and **4** are reported[14] as agonists with a rank order of agonist potency identical with our results. Thus, introduction of a double bond to the imidazoline ring of **1**, as in **3**, and addition of a benzylic hydroxyl group to **3**, as in **4**, results in a reduced inhibitory potency of the molecule. Analogue **3** also blocked aggregatory and secretory responses to ADP, AA, and U46619, suggesting additional site(s) of action beyond the α_2-adrenoceptor; the inhibitory mechanism(s) for **3** were not characterized further in our studies.

Using primary wave aggregation by epinephrine as an index of α_2-adrenoceptor interactions in human platelets, we observed that placement of a fluorine atom at the 2-, 5-, or 6-positions of the benzyl group of dihydroxytolazoline (**1**) did not modify the inhibitory potency to a significant degree. These compounds also did not block platelet activation by other inducers of the prostaglandin pathway, suggesting that they are acting as selective antagonists at α_2-adrenoceptors in human platelets. Whereas each imidazoline analogues is an inhibitor of epinephrine-induced platelet activation, they act as full or partial agonists in the other adrenoceptor tissues, and possess an agonist affinity in rat vascular α_1-adrenoceptors which is at least 1000-fold higher than our findings in platelets. In this regard, the substantial reduction in potency of the desfluoro **1** and fluoro catecholimidazolines (**5**–**7**) in this α_2-adrenoceptor system agrees favorably with the in vivo

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findings of Nichols et al.[15] in which these compounds are some 30-fold more selective for α_1 versus α_2-adrenoceptor activities. However, it should be noted that like our results obtained with platelets, relatively small differences in potency exist between 1 and its fluorinated analogues in isolated rat thoracic aorta,[14] and that this data differs significantly from their in vivo α_1- and α_2-adrenoceptor effects in pithed rats.[15]

Our results with the 4-substituted catecholimidazolines show that there is a high degree of stereoselectivity for the blockade of epinephrine-mediated primary wave aggregation, and that *S*-8 and *R*-8 were equally active as an antagonist and agonist of α_2-adrenoceptor sites in platelets, respectively. The order of inhibitory potency of *S*-8 > racemic-8 ≫ *R*-8 against primary wave aggregation by epinephrine is consistent with the proposal of a selective interaction with common receptor sites, and the competitive blockade of epinephrine-induced aggregation by *S*-8 clearly suggests that these compounds interact through α_2-adrenoceptor sites. The high isomeric inhibitory ratio ($S \gg R$) differs remarkably from previous studies in vascular α_1-adrenoceptors wherein only a small isomeric activity ratio was observed.[14,23] The qualitative and quantitative differences between *S*-8 and *R*-8 suggest that the absolute configuration in 4-substituted catecholimidazolines plays a major role in the activation of α_2-adrenoceptors in platelets.

α-Adrenoceptors in platelets, although predominantly classified as an α_2-system,[19,24,25] clearly behave differently to catecholimidazolines and catecholimidazoles as compared to their effects in other vascular α_1- and α_2-adrenoceptor systems. Others have proposed that platelets possess a mixed α_1- and α_2-adrenoceptor population[19] or have a specific α_2-adrenergic receptor subtype α_2-A which shows a greater affinity to oxymetazoline.[26] Ruffolo and co-workers[2,3,15] have previously proposed that benzylimidazolines and phenethylamines interact either with different sites on a common receptor or with different types of α-adrenoceptors. Whereas in other in vivo and in vitro α-adrenoceptor systems,[14,15] each of these compounds acted as a partial or full agonist, we found that with the exception of 4 and *R*-8, all remaining catecholimidazole and catecholimidazoline analogues functioned as antagonists of α-adrenoceptor-mediated platelet activation. Moreover, several of the compounds reversed the PGE_1-mediated inhibition of ADP-induced aggregation, suggesting that they stimulate the α_2-mediated inhibition of adenylate cyclase. Thus, like other imidazolines[17,19-21] each of the analogues (1–7) may be described as partial agonists for α_2-adrenoceptor sites in platelets. To explain these findings, platelets may possess either a different subtype[26] or lack spare receptors for interaction with imidazole or imidazoline analogues.

Ahn et al.[21] noted that the presence of a benzylic hydroxyl group is essential for full stimulatory activity of catecholimidazolines in platelets,[21] an effect that has also been shown to be important with the catecholimidazole analogue 4, in the present study. In addition, we have reported that stereochemistry plays an important role for the agonist properties of 4-substituted catecholimidazolines; only *R*-8 shows agonist activity. Further, *R*-8 represents a unique imidazoline in that it possesses potent aggregatory activity yet lacks a benzylic hydroxyl group. Moreover, neither the site of substitution of the imidazoline ring (2- or 4-position) nor nature of the heterocyclic ring (either imidazole or imidazoline) is particularly important in determining the activity of agonists within this chemical series in this α_2-adrenoceptor system. Because of the intriguing results with 4-substituted imidazolines showing both agonist and antagonist activity, we plan to continue our work to establish the structural criteria for agonist and antagonist activity on α_2-adrenoceptors in platelets.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared data were collected on a Beckman 4230 spectrophotometer. The NMR spectra were recorded on a IBM AF-250 spectrometer, a Brucker HX-90E NMR spectrometer, or an IBM AF-270 spectrometer and reported in parts per million. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, interpretation, and coupling constant (hertz). The mass spectra were obtained with a Kratos MS-25 RFA mass spectrometer or at The Ohio State University Chemical Instrument Center, by use of a VG 70-2505 or a Kratos MS-30 mass spectrometer. All organic solvents were appropriately dried and/or purified prior to use.

2-[α-Hydroxy-3,4-bis(benzyloxy)benzyl]imidazole Hydrochloride (11). To a solution of *N*-(diethoxymethyl)imidazole (**9**) (38 g, 0.224 mol) in anhydrous THF (500 mL) was added *n*-BuLi (73 mL of 2.6 M solution in hexane) with stirring and cooling in a dry ice–acetone bath under argon atmosphere. The resulting mixture was stirred for 1 h at −60 to −70 °C followed by dropwise addition of 3,4-bis(benzyloxy)benzaldehyde (**10**) (71 g, 0.223 mol) in THF (200 mL) over 30 min, and the mixture was then stirred for an additional 1 h at room temperature. To the resulting mixture was added 500 mL of 1% HCl, and the organic layer was separated from the aqueous layer and dried over anhydrous $MgSO_4$. Evaporating the solvent in vacuo gave a viscous oil product which solidified upon the addition of ether. The solid was recrystallized from EtOH to yield 64 g (74%) colorless crystals: mp 159–160 °C; ^1H NMR (CD_3OD) δ 7.5–7.2 (m, 10 H), 7.1–6.9 (m, 3 H), 6.94 (s, 2 H), 5.76 (s, 1 H), 5.11 (s, 4 H). Anal. ($C_{24}H_{22}N_2O_3$) C, H, N.

2-(3,4,α-Trihydroxybenzyl)imidazole Hydrochloride (4). The imidazole hydrochloride salt 11 (2.12 g, 5 mmol) was treated with Pd/C (10%, 200 mg) and hydrogen (45 psi) in EtOH (50 mL) for 3 h. Filtration and evaporation of the solvent gave a viscous oil, which was taken up in a mixture of EtOH, acetone, and ether and then kept in a refrigerator to afford 0.73 g (60%) of colorless crystals of 4: mp 148–150 °C; ^1H NMR (D_2O) δ 7.42 (s, 2 H), 7.1–6.8 (m, 3 H), 6.06 (s, 1 H). Anal. ($C_{10}H_{11}ClN_2O_3$) C, H, N.

2-(3,4-Dihydroxybenzyl)imidazole Hydrochloride (12). Trimethylsilyl chloride (2.2 g, 20 mmol) was added to a mixture of 11 (3.86 g, 10 mmol) and triethylamine (2.1 g, 20 mmol) in 100 mL of CH_2Cl_2. The resulting solution was stirred for 30 min at room temperature, refluxed for 30 min, and washed with brine (100 mL). After drying over anhydrous $MgSO_4$, the solvent was removed to give an oil, which solidifed upon addition of ether and the solid was recrystallized from CH_2Cl_2–*n*-hexane to yield 3.94 g (86%) of colorless crystals of trimethylsilyl derivative, mp 122–124 °C.

A mixture of 1.5 g of trimethylsilyl derivative, 3 g of triethylsilane, and 3 g of trifluoroacetic acid in 20 mL of toluene was stirred for 3 days at room temperature and evaporated to give a residue, which was taken up in 50 mL of $CHCl_3$, washed with saturated $NaHCO_3$, and dried with anhydrous Na_2CO_3. Removing the solvent in vacuo afforded an oil which was dissolved in a small amount of ethyl acetate and toluene. The resulting solution was allowed to sit at room temperature and yielded a precipitate (0.73 g, 61%), mp 120–123 °C. A solution of 500 mg (1.35 mmol) of the imidazole in 20 mL of CH_2Cl_2 was saturated with HCl gas, and the resulting solution was placed in a refrigerator for 3 h. The solvent was removed to give an oil which was taken up in ethyl acetate and placed in a dry ice–acetone bath. The resulting solid was collected by filtration and recrystallized from CH_2Cl_2–ethyl acetate to give 490 mg (89%) of the imidazole hydrochloride 12:

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mp 68–70 °C; ^{1}H NMR ($CDCl_3$) δ 7.4–7.1 (m, 10 H), 7.0–6.6 (m, 3 H), 6.82 (s, 2 H), 5.13 (s, 2 H), 4.95 (s, 2 H), 4.22 (s, 2 H). Anal. ($C_{24}H_{23}N_2O_2Cl·0.4H_2O$) C, H, N.

2-(2,3-Dihydroxybenzyl)imidazole Hydrochloride (3). A mixture of 1.0 g (2.4 mmol) of **12** in 30 mL of EtOH was hydrogenated with 100 mg of 10% Pd/C at 45 psi of hydrogen at room temperature for 2.5 h. Filtration and removal of the solvent in vacuo gave a solid which was taken up in EtOH. Ether was added to yield 0.39 g (69%) of colorless crystals of **3**: mp 182–183 °C; ^{1}H NMR (CD_3OD) δ 7.4 (s, 2 H), 6.7 (d, J = 7.9 Hz, 1 H), 6.68 (d, J = 1.9, 1 H), 6.57 (dd, J = 7.9 and 1.9 Hz, 1 H), 4.15 (s, 2 H). Anal. ($C_{10}H_{11}N_2O_2Cl$) C, H, N.

2-(3,4-Dihydroxy-6-fluorobenzyl)imidazoline Hydrochloride (7). To a solution of 2.9 g (8.34 mmol) of the nitrile **15** in 20 mL of dry benzene was added 0.5 g (10.8 mmol) of ethanol, and HCl gas (0.5 g, 13.7 mmol) was passed into the solution with cooling in an ice bath. The resulting solution was stirred at room temperature for 1 h and then kept in a refrigerator for 20 h. The mixture was then poured into 200 mL of ether. Filtration, washing with ether, and drying yielded the desired imidate (3.3 g, 92%), mp 127–128 °C.

Ethylenediamine (3.0 g, 5 mmol) was added to a solution of the imidate salt (430 mg, 1 mmol) in 15 mL of dry methanol at room temperature and the resulting mixture was stirred for 0.5 h at room temperature and then refluxed for 1 h. Removing the solvent in vacuo gave a residue which was taken up in 30 mL of CH_2Cl_2 and washed with 20 mL of 10% NaOH. The aqueous layer was extracted with 20 mL of CH_2Cl_2. The combined organic layer was washed with 20 mL of water, dried over Na_2CO_3, and evaporated to give a solid which was recrystallized from n-hexane–CH_2Cl_2 to afford 365 mg (94%) of the imidazoline.

To a suspension of 2.5 g (6.4 mmol) of the imidazoline in 10 mL of benzene and 10 mL of CH_2Cl_2 was added HCl gas, and the solution was cooled in an ice bath until the mixture was clear. The resulting solution was stirred for 30 min to afford crystals, and to this mixture was added 10 mL of ether. The crystals that formed were collected and washed with ether and recrystallized from $CHCl_3$–toluene to yield 2.57 g (94%) of the imidazoline hydrochloride salt. The salt was dissolved in 50 mL of ethanol and 0.5 g of 10% Pd/C was added and the mixture was reduced under hydrogen (45 psi) in a Parr shaker apparatus for 3 h. Filtration of the mixture and evaporation of ethanol gave a colorless solid, which was recrystallized from CH_3OH–Et_2O to yield 0.78 g (96%) of catecholimidazoline hydrochloride (**7**): mp 150–151 °C; ^{1}H NMR (CD_3OD) δ 6.72 (d, J = 7.33 Hz, 1 H), 6.59 (d, J = 10.9 Hz, 1 H), 3.90 (s, 4 H), and 3.75 (s, 2 H). Anal. ($C_{10}H_{12}FClN_2O_2$) C, H, N.

The preparation of the 2-fluoro and 5-fluoro analogues **5** and **6** was carried out in the same manner as that described for the preparation of **7** using the previously described nitriles **13** and **14**.[8] The fluoro analogue 2-(3,4-dihydroxy-2-fluorobenzyl)-imidazoline hydrochloride (**5**) was isolated in a 83% yield, mp 223–225 °C, and 2-(3,4-dihydroxy-5-fluorobenzyl)imidazoline hydrochloride (**6**) was isolated in an 82% yield, mp 193–195 °C. Anal. ($C_{10}H_9FN_2O_2$) C, H, N.

5-(Cyanomethyl)-4-fluoroveratrole (17). A mixture of 14 g (90 mmol) of 4-fluoro-3,4-dimethoxybenzene (**16**),[27] 9 of formaldehyde (37%), and 40 mL of glacial acetic acid was slowly bubbled with HCl gas for 1 h. The resulting solution was poured into 300 mL of H_2O and the mixture was extracted with ether (3 × 10 mL). The ether layer was washed with H_2O, dried ($MgSO_4$), and purified by silica gel flash chromatography with n-hexane–EtOAc (9:1) to yield 12.1 g (66% yield) of solid benzyl chloride.

A mixture of 9 g (71 mmol) of benzyl chloride and 2.7 g (55 mmol) of NaCN in 150 mL of dried DMSO was stirred for 1.5 h at room temperature. The resulting mixture was poured into 500 mL of H_2O, extracted with ethyl acetate (2 × 150 mL), and dried over $MgSO_4$. Evaporation of the solvent in vacuo and crystallization of the solid in n-hexane–CH_2Cl_2 gave 7.8 g (91%) of the desired cyanide: mp 115–116 °C; ^{1}H NMR $CDCl_3$) δ 6.84 (d, J = 6.9 Hz, 1 H), 6.65 (d, J = 10.81 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), and 3.7 (s, 2 H). Anal. ($C_{10}H_{10}FNO_2$) C, H, N.

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4,5-Bis(benzyloxy)-2-fluorobenzyl Cyanide (15). To a solution of 1.95 g (10 mmol) of cyanide **17** in 20 mL of CH_2Cl_2 was added 20 mL of BBr_3 (1 M in CH_2Cl_2) with cooling in an ice bath followed by stirring for 3 h at room temperature under argon. The resulting solution was poured into 50 mL in cold ammonium hydroxide (10%) and the resulting organic layer was separated and extracted with H_2O (2 × 20 mL). The aqueous layers were combined and acidified with concentrated HCl and extracted with ethyl acetate (3 × 30 mL) and dried (Na_2SO_4). The ethyl acetate solution was diluted with the same volume of CH_2Cl_2 and passed through a silica gel column and evaporated to give a solid which was recrystallized from n-hexane–ethyl acetate to afford 1.29 g (83%) of colorless needles of the catechol derivative, mp 130 °C.

A mixture of 330 mg (1.98 mmol) of the catechol, 600 mg (4.3 mmol) of K_2CO_3, 100 mg (0.67 mol) of NaI, and 800 mg (6.3 mol) of benzyl chloride was placed into 50 mL of acetone. The mixture was refluxed for 20 h followed by treatment with charcoal, filtration, and evaporation to give a solid. The solid was purified by flash chromatography over silica gel with n-hexane–ethyl acetate (15%) to yield 587 mg (86%) of cyanide **15**: mp 82–83 °C; ^{1}H NMR ($CDCl_3$) δ 7.37–7.25 (m, 10 H), 6.96 (d, J = 6.43 Hz, 1 H), 6.70 (d, J = 10.99 Hz, 1 H), 5.11 (s, 4 H), and 3.61 (s, 2 H). Anal. ($C_{22}H_{18}FNO_2$) C, N, H.

(*S*)-*N*-(*tert*-Butyloxycarbonyl)-3,4-bis(benzyloxy)-phenylalaninamide (20). A mixture of 33 g (106 mmol) of (*S*)-BOC-Dopa-OCH_3, benzyl bromide (28 g, 220 mmol), K_2CO_3 (33 g, 239 mmol), and NaI (1.5 g, 10 mmol) in 500 mL of EtOH was refluxed for 3 h. The solvent was evaporated and the residue was taken up in 1500 mL of ethyl acetate and washed with 500 mL of 10% HCl followed by brine and dried over $MgSO_4$. Removing the solvent gave a solid which was taken up in 500 mL of methanol and refluxed with 300 mL of 2 N NaOH for 1 h followed by cooling to room temperature and the addition of 60 mL of concentrated HCl to form a precipitate. Filtration and recrystallization from CH_2Cl_2–n-hexane yielded 133.5 g of the (*S*)-BOC-Dopa-$(Bn)_2$ (66%), mp 139–141 °C (lit.[9] mp 140–142 °C).

To a solution of ethyl chloroformate (7.2 g, 66 mmol) in 200 mL of CH_2Cl_2 was added dropwise a solution of 28.5 g (60 mmol) of (*S*)-BOC-Dopa-$(Bn)_2$ and 6.4 g (63 mmol) of triethylamine in 500 mL of CH_2Cl_2 over a 30-min period in a dry ice–acetone bath. The reaction mixture was stirred for an additional 1.5 h at 0 °C and ammonia was bubbled through the cold mixture for 30 min. After stirring an additional 30 min at room temperature, 500 mL of $CHCl_3$ was added and the mixture was washed with water followed by a saturated solution of sodium bicarbonate and dried over Na_2SO_4. Filtration and evaporation of the $CHCl_3$ solution gave a solid that was recrystallized from EtOH–ethyl acetate to give 27.0 g of amide **20** (95%): mp 175–177 °C; ^{1}H NMR ($CDCl_3$) δ 7.5–7.2 (m, 10 H), 7.0–6.7 (m, 3 H), 5.10 (s, 2 H), 5.06 (s, 2 H), 4.23 (bq, 1 H), 2.95 (t, 2 H), 1.35 (s, 9 H); $[\alpha]_D$ = +13.0° (38.6 mg/10 mL of MeOH). Anal. ($C_{28}H_{32}N_2O_5$) C, H, N.

The *R* isomer of **20** was prepared in the same manner as the *S* isomer with (*R*)-BOC-Dopa-OCH_3: mp 177–178 °C; $[\alpha]_D$ = −13.4° (62.7 mg/10 mL of MeOH). Anal. C, H, N.

The racemic mixture of **20** was prepared in the same fashion as the *S* isomer with racemic BOC-Dopa-OCH_3, mp 166–167 °C. Anal. C, H, N.

(*S*)-2-[3,4-Bis(benzyloxy)benzyl]ethylenediamine Dihydrochloride (21). A mixture of 9.0 g (18.9 mmol) of **20**, 19 mL of trifluoroacetic acid, and 190 mL of CH_2Cl_2 was stirred at room temperature for 3 h, and the resulting mixture was evaporated to give an oily residue, which was dissolved in ethyl acetate, washed with saturated $NaHCO_3$, and dried (Na_2SO_4). The solvent was removed in vacuo and the remaining solid was recrystallized from $CHCl_3$–hexane to yield 6.71 g (94%) of the unprotected phenylalaninamide, mp 126–128 °C.

To a solution of 5.7 g (15 mmol) of the amide in 50 mL of dry THF was added 50 mL (1 M solution in THF) of diborane over a 30-min period with cooling in an ice bath. The resulting mixture was refluxed for 15 h followed by cooling in an ice bath. To the mixture was added 10 mL of methanol and the mixture was refluxed for 3 h. The mixture was cooled and the solvent was then removed in vacuo. The resulting residue was taken up in 20 mL of methanol and 3.9 g of oxalic acid in 20 mL of methanol was added and the resulting precipitate was isolated by filtration and washed with ethanol and ether and dried to give 7.8 g (95%)

of the ethylenediamine oxalate, dp 169–170 °C.

To a suspension of 13.3 g (6.08 mmol) of the oxalate in 50 mL of methanol was added HCl gas until the mixture became clear at room temperature. Evaporation of the solvent and recrystallization from ethanol gave 2.43 g (92%) of **21**: mp 234–236 °C; ^{1}H NMR (D_2O) δ 7.5–7.2 (m, 10 H), 7.1–6.8 (m, 3 H), 5.16 (s, 2 H), 5.13 (s, 2 H), 3.7–3.5 (m, 1 H), 3.3–2.9 (m, 4 H); $[\alpha]_D$ = −15.6° [98.8 mg/10 mL (1:1, MeOH–H_2O)]. Anal. ($C_{23}H_{28}Cl_2N_2O_2$) C, H, N.

The *R* isomer of **21** was prepared in the same manner as for the *S* isomer, dp 232–234 °C; $[\alpha]_D$ = +15.5° [79.4 mg/10 mL (1:1, MeOH–H_2O)]. Anal. C, H, N.

The racemic mixture of **20** was prepared in the same manner as for the *S* isomer, mp 223–225 °C. Anal. C, H, N.

(*S*)-4-[3,4-Bis(benzyloxy)benzyl]imidazoline Oxalate (22). A mixture of 3.7 g (8.5 mmol) of the diamine **21** and 50 mL of H_2O along with 1 g (25 mmol) of NaOH was shaken well and extracted with 50 mL of CH_2Cl_2. The organic layer was dried over $NaHCO_3$ and evaporated to give an oily residue of free diamine. The residue was taken up in 50 mL of CH_2Cl_2, and to this was added 3.56 g (32.4 mmol) of ethyl formimidate hydrochloride, and the resulting mixture was stirred for 15 h at room temperature under argon atmosphere. The mixture was then washed with 30 mL of 5% NaOH and H_2O and dried with Na_2CO_3. The solution was filtered, and to the filtrate was added 1.10 g (8.7 mmol) of the oxalic acid dihydrate (1.1 g, 8.7 mmol) in 10 mL of MeOH. Removing the solvent in vacuo gave a solid that was recrystallized from 90% EtOH to yield 2.6 g (70%) imidazoline oxalate **22**: dp 186–188 °C; ^{1}H NMR (CD_3OD) δ 8.14 (s, 1 H), 7.5–7.2 (m, 10 H), 7.0–6.8 (m, 3 H), 5.14 (s, 2 H), 5.10 (s, 2 H), 4.6–4.3 (m, 1 H), 4.0–3.6 (m, 2 H), 2.86 (d, *J* = 6.4 Hz, 2 H); $[\alpha]_D$ = −72.7° (21.9 mg/10 mL of 80% MeOH). Anal. ($C_{26}H_{26}N_2O_6$) C, H, N.

The *R* isomer of **22** was prepared in a manner similar to that for the *S* isomer, dp 185–186 °C; $[\alpha]_D$ = +73.1° (20.8 mg/10 mL of 80% MeOH). Anal. C, H, N.

The racemic mixture of **22** was also prepared according to the procedure for the *S* isomer, dp 185–186 °C. Anal. C, H, N.

(*S*)-4-(3,4-Dihydroxybenzyl)imidazoline Oxalate (8). The imidazole oxalate **22** (0.9 g, 2 mmol) in 50 mL of MeOH was reduced with 0.9 g of 10% Pd/C under hydrogen at 50 psi for 3 h to yield 0.46 g (84%) of the catechol imidazoline *S*-**8**, and it was recrystallized from MeOH to give a solid: dp 180–182 °C; ^{1}H NMR (CD_3OD) δ 8.19 (s, 1 H), 6.77–6.49 (m, 3 H), 4.60–4.35 (m, 1 H), 4.01–3.51 (m, 2 H), 2.78 (d, *J* = 6.3, 2 H); $[\alpha]_D$ = −114.5° (10.0 mg/10 mL of 70% MeOH). Anal. ($C_{12}H_{14}N_2O_6$) C, H, N.

R isomer **8** was prepared in a manner similar to that for the *S* isomer: dp 179–182 °C; $[\alpha]_D$ = +116.8° (21.8 mg/10 mL of 70% MeOH). Anal. C, H, N.

The racemic mixture of **8** was prepared in a manner similar to that for the *S* isomer, dp 210–212 °C. Anal. C, H, N.

The optical purity of *S*-**8** and *R*-**8** was determined with the aqueous chiral shift reagent CoATP using the procedure of DeBernardis and co-workers.[28] The NMR studies indicate the optical purity to be >98%.

Platelet Antiaggregatory Activities. Blood was collected from normal volunteers who reported to be free of medication for 10 days prior to blood collection. Platelet-rich plasma was prepared with use of 1.1 M citrate as anticoagulant (9:1, v/v) as described previously. Aggregation studies were performed according to the turbidometric method of Born[29] in a Payton or Chronolog dual channel aggregometer interfaced to an Apple microcomputer for acquisition, quantitation, presentation, and management of data.[30] Each compound was tested for the ability to produce aggregation alone in platelets preincubated with 1 mM aspirin for 1 min. For inhibition studies, selected inducers were used at the minimum concentrations required to stimulate maximal aggregation responses. Inhibitors were added 1 min prior to induction of platelet activation, and inhibitory concentration-50 (IC_{50}) values for each compound were determined for maximal changes in amplitude of light transmittance after 6 min for ADP and epinephrine or 4 min for U46619 and arachidonic acid (AA). Control aggregation (percent transmittance) responses (mean ± SEM) were 82 ± 2, 82 ± 3, 79 ± 2, and 81 ± 5 for ADP, epinephrine, AA, and U46619, respectively. Values obtained for ADP and epinephrine primary wave transmittances were 44 ± 4 and 23 ± 1, respectively. Aspirin (1 mM) was routinely added to platelet preparations in experiments to examine drug effects on the primary wave aggregation response to epinephrine and on U46619-induced aggregation and secretion responses. Secretion of the contents of platelet-dense granules was measured by monitoring the release of radioactivity from platelets prelabeled with [^{14}C]serotonin.[21] Control secretion (mean ± SEM) was 44 ± 3, 50 ± 2, 47 ± 3, and 27 ± 2% for ADP, epinephrine, AA, and U46619, respectively. In experiments designed to examine the nature of the inhibition of primary wave aggregation to epinephrine by *S*-**8**, the shifts in the effective concentration-50 (EC_{50}) values of epinephrine were evaluated in the presence of varying concentrations of this drug. For those studies designed to evaluate the ability of each analogue to reverse PGE_1 (1 μM) mediated inhibition of ADP aggregation, a 2-min preincubation time for the drug was used, and PGE_1 was added 0.5 min before the inducer.

Data Analyses. EC_{50} and IC_{50} values of drugs were analyzed by a computer program using individual plots of percent response or percent inhibition, versus log concentration and expressed as EC_{50} or pIC_{50} values, respectively. Shild plots were analyzed by computer according to the method of Tallarida and Murray.[31] Data were expressed as the mean ± SEM.

Registry No. **3**, 116235-68-8; **3**·HCl, 125227-91-0; **4**, 125227-90-9; **4**·HCl, 125227-92-1; **5**, 116235-69-9; **5**·HCl, 125227-93-2; **6**, 116218-75-8; **6**·HCl, 125227-94-3; **7**, 116218-76-9; **7**·HCl, 125227-95-4; (*S*)-**8**, 116218-77-0; (*S*)-**8**·oxalate, 125227-96-5; (*R*)-**8**, 116218-78-1; (*R*)-**8**·oxalate, 125228-19-5; (±)-**8**, 116297-62-2; (±)-**8**·oxalate, 125249-51-6; **9**, 61278-81-7; **10**, 5447-02-9; **11**, 125228-04-8; **11**·HCl, 125227-97-6; **12**, 125228-06-0; **12**·HCl, 125227-98-7; **13**, 103138-24-5; **14**, 104716-77-0; **15**, 125227-99-8; **15** (ethyl imidate), 125228-07-1; **16**, 398-62-9; **17**, 91407-49-7; (*R*)-**19**, 125279-74-5; (*S*)-**19**, 37169-36-1; (±)-**19**, 37169-36-1; (*S*)-**20**, 125228-00-4; (*R*)-**20**, 125249-50-5; (±)-**20**, 125353-55-1; (±)-**20**·HCl, 125353-56-2; (*S*)-**21**, 125228-13-9; (*S*)-**21**·2HCl, 125228-01-5; (*S*)-**21**·xoxalate, 125228-14-0; (*R*)-**21**, 125228-16-2; (*R*)-**21**·2HCl, 125228-15-1; (*S*)-**22**, 125228-02-6; (*S*)-**22**·oxalate, 125228-03-7; (*R*)-**22**, 125228-17-3; (*R*)-**22**·oxalate, 125228-18-4; (±)-**22**, 125279-75-6; (±)-**22**·oxalate, 125279-76-7; (*S*)-BOC-DOPA-$(Bn)_2$, 125228-11-7; 2-[[3,4-bis(benzyloxy)phenyl](trimethylsilyloxy)-methyl]imidazole, 125228-05-9; 2-[3,4-bis(benzyloxy)-6-fluorobenzyl]imidazoline, 125228-08-2; 2-[3,4-bis(benzyloxy)-6-fluorobenzyl]imidazoline hydrochloride, 125228-09-3; 2-(chloromethyl)-4,5-dimethoxy-1-fluorobenzene, 91407-48-6; 2-(chloromethyl)-4,5-dihydroxy-1-fluorobenzene, 125228-10-6; (*S*)-3,4-bis(benzyloxy)phenylanaline amide, 125228-12-8.

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